Organic LETTERS

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One-Pot Organocatalytic Enantioselective Michael–Michael–Aldol–Henry Reaction Cascade. A Facile Entry to the Steroid System with Six Contiguous Stereogenic Centers

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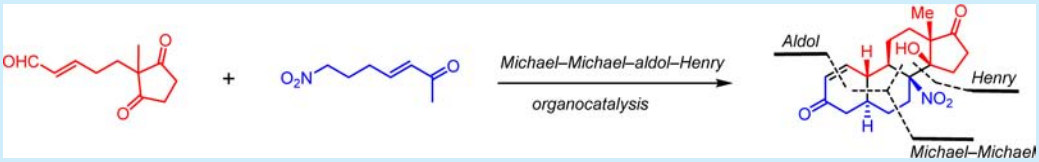
Supporting Information



ABSTRACT: An expedited method has been developed for the enantioselective synthesis of highly functionalized steroid systems containing six contiguous stereogenic centers with high enantioselectivities (99% *ee*). The one-pot methodology comprises a cascade of organocatalytic Michael–Michael–aldol–Henry reactions of 7-nitrohept-3-en-2-one and 5-(1-methyl-2,5-dioxocyclopentyl)pent-2-enal. The structure and absolute configuration of the products were confirmed by X-ray analyses of appropriate products.

Steroids have long played a pivotal role in medicinal chemistry due to their definitive polycyclic structures and various biological activities (Figure 1). The interest in the wide

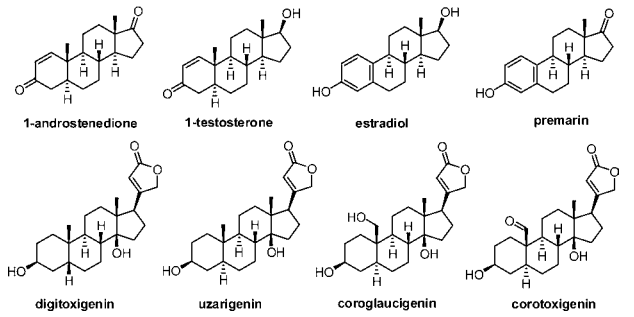


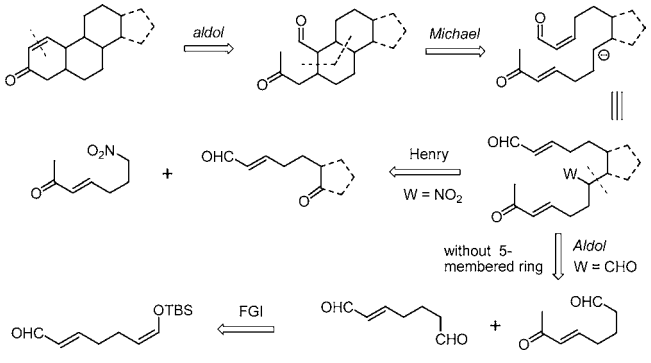
Figure 1. Selected examples of natural and biologically active steroids.

ranging investigations of steroids and their preparation in the mid-20th century continues to the present day. The synthesis of these polycyclic compounds still attracts the attention of chemists[1] and pharmacologists,[2] with particular focus on the processes that control steroid synthesis. These intriguing synthetic methodologies for constructing the steroidal skeleton include transition-metal-catalyzed reactions,[3] polyolefin carbocyclizations,[4] Diels–Alder reactions,[5] and enantioselective approaches.[6]

Asymmetric organocatalysis has undergone a resurgence of interest,[7] especially as inspired by the pioneering Hajos–Parrish–Eder–Sauer–Wiechert reaction[8] and the Wieland–Miescher ketone synthesis.[9] After decades of dormancy,[10] asymmetric organocatalyzed reactions have become a burgeoning topic in contemporary synthetic chemistry. Despite the extensive applications of the Hajos–Wiechert–Parrish ketone and Wieland–Miescher ketone[11] in traditional steroid syntheses, the demonstration of a modern asymmetric organocatalytic cascade for the synthesis of the steroid framework has garnered little attention and examples remain rare.[12]

Prompted by the aforementioned background and in an effort to extend our studies on organocatalyzed annulations,[13,14] we envisioned that a cascade of organocatalytic reactions[15] might provide a useful protocol for the formation of a highly functionalized steroid system containing multiple contiguous stereogenic centers (Scheme 1). Retrosynthetic disconnection of estrene-3-one or tetradecahydrophenanthren-3-ene-2-one via aldol and Michael transforms led to the 13-oxotetradeca-2,11-

Scheme 1. Retrosynthetic Analysis



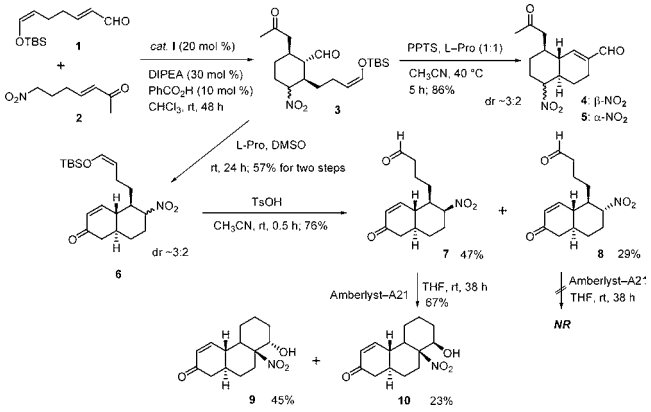
Received: April 7, 2014
Published: May 5, 2014

   dx.doi.org/10.1021/ol501011t | *Org. Lett.* 2014, 16, 2724–2727

dienal derivative (Scheme 1). Subsequently, aldol transformation disconnection of the derivative, with an aldehyde serving as the electron-withdrawing group, and the transformation of the functional group by protection of the aldehyde would provide 7-[(trimethylsilyl)oxy]hepta-2,6-dienal and 8-[(trimethylsilyl)oxy]octa-3,7-dien-2-one. Alternatively, Henry transform disconnection of the intermediate, with the nitro group as the electron-withdrawing group, may give rise to the 7-nitrohept-3-en-2-one and 5-(2-oxocyclopentyl)pent-2-enal.

At the outset of the study, as shown in Scheme 1, reaction of 7-[(trimethylsilyl)oxy]hepta-2,6-dienal (**1**) and 7-oxooct-5-enal with the Jørgensen–Hayashi catalyst (**I**)[16] and acetic acid under various reaction conditions gave a complicated mixture of products, arising from the self-condensation of dienal (**1**).[17] When we focused our attention on the nitro derivatives (Scheme 2), the results were more promising. Reaction of enal

Scheme 2. Reactions toward Tetradecahydrophenanthren-3-ene-2-one System



1[18] and nitroenone **2**[19] with 20 mol % of the Jørgensen–Hayashi catalyst (**I**), benzoic acid (10 mol %), and Hünig base (DIPEA, 30 mol %) in $CHCl_3$ at ambient temperature for 48 h afforded an inseparable diastereoisomeric mixture of the ketoaldehyde **3** in 75% yield in a *ca.* 3:2 ratio.[20] Treatment of the ketoaldehyde **3** with pyridinium *p*-toluenesulfonate (PPTS) and L-Pro in CH_3CN at 40 °C for 5 h led to the deprotection of enolsilyl ether, followed by a subsequent aldol condensation to give an 86% yield of decalines **4** and **5**, after two reaction steps. Alternatively, exposure of **3** to L-Pro in DMSO at ambient temperature for 24 h gave a 57% yield of an inseparable diastereoisomeric mixture of nitroenone **6**, after a two-step reaction starting from enal **1** and nitroenone **2**. Deprotection of the enolsilyl ether group of **6** (TsOH, CH_3CN, rt, 30 min) provide a 47% yield of nitroaldehyde **7** and a 29% yield of **8**. Henry reaction of **7** was conducted with Amberlyst-A21 in THF at rt for 38 h to give a diastereomeric mixture of **9** and **10** (45% and 23% yield, with 94 and 93% *ee*, respectively). The structure of (+)-**9** was ascertained by single-crystal X-ray analysis (Figure 2). Surprisingly, attempted Henry reactions of **8** under the same conditions did not proceed but resulted in the recovery of **8** after a few days of reaction.

After the success of the approach to tetradecahydrophenanthren-3-ene-2-one system, **11**[21] was selected for the reaction with nitroenone **2**. The double Michael reaction of **2** and **11** was screened with a variety of organocatalysts to obtain the cyclohexane adducts **12** (Table 1). The optimization conditions are briefly summarized in Table 1. Reaction of **2** and **11** with

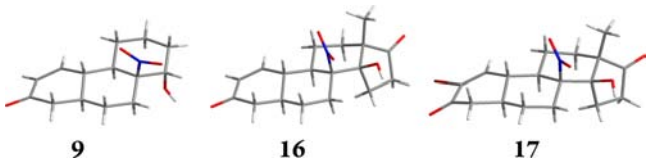
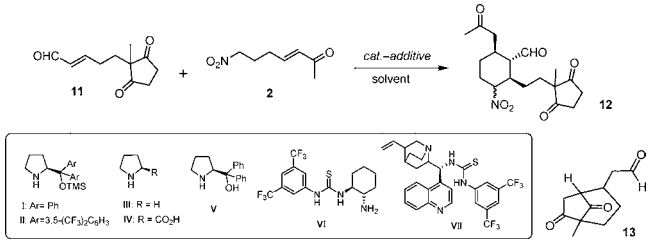


Figure 2. Stereoplots of the X-ray crystal structures of (+)-**9**, (+)-**16**, and (+)-**17**: C, gray; O, red; Br, purple.

Table 1. Screening of the Catalysts, Solvents, and Conditions for the Double Michael Reactions[a]



entry	cat.–additive	solvent	time (h)	yield[b] (%)	dr[c] (syn/anti)
1	**I**–$PhCO_2H$	$CHCl_3$	3	0[d]	na
2	**I**	$CDCl_3$	48	0[d]	na
3[e]	**I**–DBU	$CHCl_3$	30	14[f]	nd
4	**I**–DIPEA	$CHCl_3$	24	53	54:46
5	**I**–DIPEA–$PhCO_2H$	$CHCl_3$	18	48	55:45
6	**I**–DIPEA	Toluene	108	44	50:50
7	**I**–DIPEA	EtOH	23	35	47:53
8	**I**–DIPEA	CH_3CN	17	21	47:53
9	**I**–DIPEA	CH_2Cl_2	28	33	48:52
10	**I**–DIPEA	THF	96	nr	na
11	**I**–DIPEA	DMF	96	13	16:84
12[e]	**I**–DIPEA	$CHCl_3$	56	63	56:44
13[e,g]	**I**–DIPEA	$CHCl_3$	48	69	52:48
14[e]	**I**–Et_3N	$CHCl_3$	48	56	55:45

[a]Unless otherwise noted, the reactions were performed with 0.2 M of **2** and with 1.5 equiv of **11** at 28 °C, using 20 mol % of the catalyst and additive at 28 °C in a vial containing the appropriate solvent. [b]Isolated yields of **12**. [c]Determined by ^1H NMR of the crude reaction mixture. [d]Decomposition of **11** with no products observed. [e]Reaction at 10 °C. [f]Along with a 37% yield of **13**. [g]Reactions were performed on a scale of 0.2 M of **2** and with 2.2 equiv of **11**. nd = not determined. na = not available. nr = no reaction.

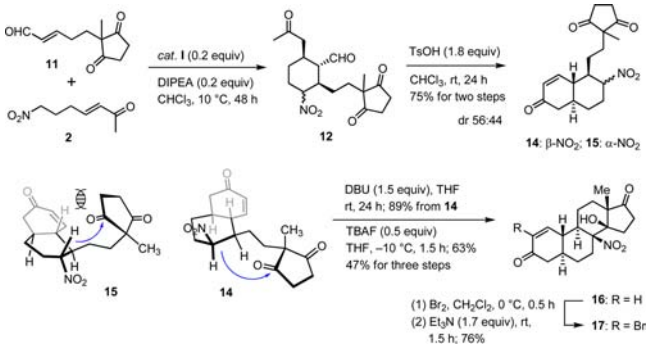
catalyst **I**–$PhCO_2H$ (20 mol %) in $CHCl_3$ at rt for 3 h afforded the self-dimerization and decomposition of **11**[17] and provided no observed product **12** (Table 1, entry 1). A similar observation was obtained for the reaction in the absence of the benzoic acid additive (Table 1, entry 2). To minimize the self-dimerization of **11** and to increase the nucleophilicity of nitroalkane **2**, several organic bases were screened. As shown in Table 1, entry 3, the reaction with **I**–DBU (20 mol %) in $CHCl_3$ at 10 °C for 30 h afforded 14% of the product **12**, however, along with a 37% yield of a side product **13** arising from the intramolecular Michael reaction of **11**. The yield of adduct **12** was increased to 53% by substituting DIPEA, a less basic base, for DBU (Table 1, entry 4). However, addition of the combinatorial additive DIPEA–$PhCO_2H$ in the reaction mixture did not help in increasing the yield (Table 1, entry 5). We conducted further attempts to optimize the double-Michael reaction with **I**–DIPEA in various solvents, but the results were fruitless (Table 1, entries 6–11). To our delight, lowering the

dx.doi.org/10.1021/ol501011t | *Org. Lett.* 2014, 16, 2724–2727

reaction temperature to 10 °C diminished the decomposition of **11** and resulted in increasing the yield to 63% after 56 h of reaction (Table 1, entry 12). Nevertheless, a further decrease in the reaction temperature to 0 °C did not improve the yield but required a longer time (72 h) to complete the reaction. With 2.2 equiv of **11**, the reaction could be completed in 48 h, providing 69% of the product (Table 1, entry 13). Replacement of DIPEA by Et_3N in the reaction did not improve the yield (Table 1, entry 14). Finally, screening of the other catalysts (**II** to **VII**) with DIPEA in the reaction gave no reaction or provided only trace amounts of products.

With the best reaction conditions in hand (Table 1, entry 13), an efficient one-pot operation of the double Michael−aldol reaction was attempted, and the results were promising with a higher overall isolated yield than the stepwise operation. Reaction of **11** and **2** with **I**−DIPEA (20 mol %) at 10 °C in $CHCl_3$ for 48 h, followed by the addition of *p*-TsOH (1.8 equiv), and stirring for an additional 24 h at rt provided 75% yields of a 56:44 ratio of nitro ketones **14** and **15**, with 98% and 99% *ee*, respectively (Scheme 3). A Henry reaction of the

Scheme 3. Reactions toward Steroid System

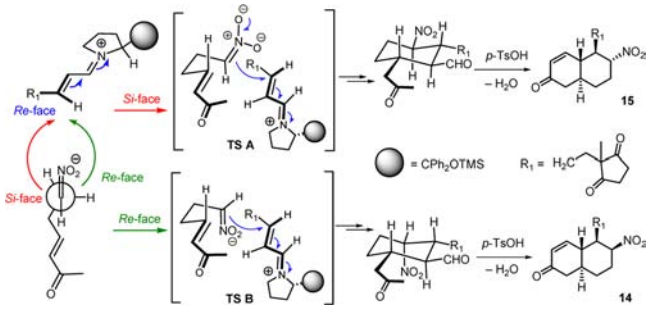


diastereomeric mixture **14** and **15** was achieved by treatment with TBAF (0.5 equiv) in THF at −10 °C for 90 min to give **16** in 63% yield with 99% *ee*. It should be noted that the Henry reaction of **14** was feasible with DBU (1.5 equiv) at rt to afford **16** in 89% yield, but required a much longer reaction time (24 h) than the reaction with TBAF.[22] However, exposure of **15** with DBU (1.5 equiv) at rt gave no reaction after 4 days. The result may be due to the fact that the large steric bulk of isomer **15** may encumber the Henry reaction (Scheme 3), as an isomerization of **15** to **14** was observed upon addition of TBAF to the reaction mixture, followed by the subsequent reaction to give **16**. Moreover, DBU was unable to trigger the isomerization of **15** owing to the steric bulk of the substrate. The structure of (+)-**16** was confirmed by X-ray analysis (Figure 2).

Later, the three-step reaction was completed in a one-pot process. Addition of the THF into the freshly prepared reaction mixture of **14** and **15** in $CHCl_3$, followed by the addition of TBAF (4 equiv) with stirring at rt for 20 h, gave a 25% yield of **16**, starting from **11** and **2**. Subsequently, we observed that the Henry reaction of **15** with TBAF in $CHCl_3$ required a longer reaction time than in THF. Consequently, evaporation of $CHCl_3$ in the freshly prepared reaction mixture of **14** and **15**, followed by the addition of THF, DBU (3.6 equiv, stirred at rt for 2 h), and TBAF (3.6 equiv, stirred at 0 °C for 20 h) afforded a 47% yield of **16**, starting from **11** and **2**. A bromo steroid derivative **17** was prepared via a sequence of bromination and elimination of **16** (Br_2, CH_2Cl_2, 0 °C, 0.5 h; Et_3N, rt, 1.5 h; 76%). The structure and absolute configuration of the product (+)-**17** were assigned unambiguously by the single-crystal X-ray analysis (Figure 2).

To account for the stereoselectivity of the transformation, we propose a plausible mechanism (Scheme 4). Initially, iminium

Scheme 4. Proposed Mechanism for the One-Pot Transformation



formation of the enamine from **11** occurs, followed by the nucleophilic attack of nitroenone **2** (from either the *Si*- or *Re* face of the nitroalkane) on the iminium activated aldehyde **11** via the *Re* face under the control of the catalyst (**TS A** or **TS B**), giving the intermediate, which spontaneously undergoes an additional Michael reaction to afford **12**. A subsequent aldol reaction of the adducts with *p*-TsOH would give the *trans*-decalines **14** and **15**. The mechanism of the Henry reaction of the *trans*-decaline diones **14** and **15** with TBAF leading to steroid **16** is elucidated in Scheme 3 (*vide supra*).

Recently, self-disproportionation of enantiomers (SDE)[23] has attracted much attention, as it demonstrates that the optical purification of enantiomerically enriched compounds can be achieved via achiral chromatography. Particularly, this subject may be related to prebiotic chemistry, providing a possible answer to a great mystery that has long puzzled scientists: what is the origin of the chirality of the molecules of living systems?[24] It is worth noting that the compounds at hand, *e.g.*, **16**, were purified by an achiral silica-gel column with collection of all fractions containing the designated product together for the analyses, but not a single fraction from the separation. Therefore, the *ee* analysis of each compound reflects the *ee* of the sum of the designated product obtained. However, the literature suggests that compounds capable of forming H-bonding would be particularly prone to exhibit a significant magnitude of SDE. We questioned if **16** possesses a substantial SDE effect. In this context, an SDE test was performed on an enantiomerically enriched 50% *ee* sample of **16**, prepared by mixing an adequate portion of (+)- and (−)-**16**,[25] and a significant magnitude ($\Delta ee \approx 24.6\%$)[26] was observed in the seven fractions collected from the achiral silica-gel chromatography. Logically, the intermolecular H-bonding interaction of **16** may play a key role in the SDE effect.

In summary, we have described a concise synthesis of optically enriched steroids, with the multifunctionalized tetracycles containing six stereogenic centers with a quaternary carbon stereocenter with high enantioselectivities (99% *ee*) by sequential organocatalytic double Michael/aldol/Henry reactions. Particularly noteworthy is the one-pot operation of the reactions at the key steps in the synthesis of estr-1-ene-3,17-dione derivatives. The structures and the absolute configuration of the products were unambiguously confirmed by single-crystal X-ray crystallographic analyses of the appropriate adducts.

dx.doi.org/10.1021/ol501011t | *Org. Lett.* 2014, 16, 2724−2727

Further applications of this protocol in the synthesis of elaborated steroid derivatives are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for compound (+)-**9**, (+)-**16**, and (+)-**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support for this study from the Ministry of Science and Technology (MOST, Taiwan) and thank the instrument center (MOST) for analyses of compounds. Thanks to Mr. Wei-Lun Huang (NCCU) and Dr. Nitin S. Dange (NCCU) for their assistance. We also thank Professor Vadim A. Soloshonok (University of the Basque Country) for the valuable suggestions.

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(18) For preparation, see Supporting Information.

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(20) Ketoaldehyde **3**, somewhat sensitive to the silica-gel chromatography, decomposed to a certain extent during the purification. For synthetic operation, these adducts were subjected to the next reaction step without further purification.

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(25) (+)-**16** and (−)-**16** were prepared from the catalyst (*S*)-**I** and (*R*)-**I**, respectively.

(26) The result produced enantiomerically enriched (62.1% ee) first and enantiomerically depleted (37.5% ee) last fractions.